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transforming domain, wherein said extracellular ligand-specific moiety selectively recognizes said selected substance, which recognition activates said intracellular signal transforming domain;

B1 (b) a transducer, wherein said transducer has an inactive and an active form which are distinct from each other, and wherein said activated intracellular signal transforming domain converts said inactive form of said transducer into said active form of said transducer; and

(c) a responsive element, wherein said responsive element is activated by said active form of said transducer, resulting in a detectable signal.

B2 21. (Amended) The biodetector of claim [7] 1, wherein said signal transforming domain [membrane signal transducer] is derived from PhoQ.

REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated June 28, 1999 are respectfully requested. The applicant petitions the Commissioner for a 3-month extension of time: a separate petition accompanies this amendment.

I. Amendments to the Specification

The Examiner has requested a substitute specification (including claims) pursuant to 37 CFR 1.125(a), because the line numbers in the left margin of the originally-filed specification do not correspond to the actual lines of text. Enclosed herewith is the requested substitute specification, together with the originally-filed claims. The claims submitted with the substitute specification do not reflect any amendments made during the prosecution of this application, and thus should not be construed as replacing the presently-pending claims, as amended herein and by the Preliminary Amendment filed on November 12, 1998.

II. Amendments to the Claims

Claim 1 has been amended to delete "the" to improve antecedent basis.

Claim 21 has been amended to replace --signal transforming domain-- with "membrane signal transducer". The amendment finds support in the specification on page 15, lines 24-30.

The amendments to the claims introduce no new matter into the specification. Claims 1-27 are pending in the present application; Claims 1-9 and 21-27 are under consideration.

III. Oath/Declaration

The Examiner indicated that the oath or declaration is defective because it was not signed by coinventor David A. Benaron. The Examiner requested a new oath or declaration in compliance with 37 C.F.R. §1.67(a). Enclosed herewith is a new oath or declaration signed by all coinventors in compliance with 37 C.F.R. §1.67(a).

IV. Drawings

The Examiner objected to the Drawings under 37 C.F.R. §1.84 or §1.152 for the reasons set forth in PTO Form 948. Enclosed herewith are corrected Drawings as required by PTO Form 948.

V. Restriction Requirement Issues

The Examiner indicated that the application contains claims 10-20 drawn to an invention nonelected with traverse in Paper No. 7, and that a complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action. Although the applicant intends to cancel non-elected claims in response to a Notice of Allowance, the applicant is unclear as to the basis of the Examiner's remark: the applicant's response to the restriction requirement was made without traverse, and acknowledged as such by the Examiner at the bottom of page 2 of the Office Action mailed June 28, 1999.

VI. Rejections under 35 U.S.C. §112, first paragraph

A. Biological Deposit

The Examiner has rejected claims 1-9 and 21-27, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. It is the Examiner's view that a deposit of the claimed biodetectors is required to overcome these rejections.

Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation (37 C.F.R. §1.802(b)). In the present case, the invention is directed to biodetectors formed of the following elements: (i) a signal converting element, (ii) a transducer, and (iii) a responsive element. The making of components which make up each of the above elements is described in the specification or is known in the art, and does not involve undue experimentation.

For example, the specification describes, on pages 14-16, the making of a suitable signal converting element. It provides specific examples of suitable ligand binding domains (*e.g.*, antibodies or antibody fragments), and specific examples of suitable signal transforming domains (*e.g.*, the active domain of PhoQ). Further, the specification contains three detailed examples which provide alternative approaches to constructing biodetectors according to the claimed invention (see pages 25-27). Similarly, the specification provides guidance for the making of transducers (page 16; Examples 1-3) and responsive elements (pages 16-19, Examples 1-2).

As a matter of Patent Office practice, an applicant's statements concerning enablement of the invention "must be taken as in compliance with the enabling requirement of the first paragraph of 35 U.S.C. §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi 169 USPQ 367 (C.C.P.A. 1971). Absent evidence to the contrary, the Examiner must accept the information presented by the applicant as fact.

In the present case, the Examiner has not presented any objective evidence to call into question the enablement of the present invention. In contrast, the applicant has provided detailed descriptions, together with Examples, showing how to make and use the biodetectors of the present invention.

In view of the foregoing, the applicant submits that the pending claims are in compliance with the enablement provisions the first paragraph of 35 U.S.C. §112, and that the rejection of claims 1-9 and 21-27 is inappropriate and should be withdrawn.

B. Written Description

The Examiner has further rejected claims 21,22,25 and 26 under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention, *i.e.*, as failing to comply with the Written Description requirement of U.S.C. §112, first paragraph.

References below to line numbers in the specification are made with respect to the substitute specification enclosed herewith.

Claim 21 - Claim 21 recites the limitation "said membrane signal transducer is derived from PhoQ". The Examiner asserts that the specification as originally filed does not provide support for this limitation.

Claim 21 has been amended by the present amendment to depend on Claim 1, and replace the "membrane signal transducer" with --signal transforming domain--.

Basis for the limitation of amended Claim 21 can be found, for example, on page 14, line 20 through page 16, line 9. This section, titled "The Signal-Converting Element", describes in detail the two parts of the signal-converting element, namely (i) the ligand-binding domain (or extracellular ligand-binding portion - see, e.g., page 14, lines 23-25) and (ii) the signal transforming domain (or intracellular enzymatic portion - see,

e.g., page 14, lines 23-26). In particular, page 15, lines 29-30 of the specification provide:

> "In a specific embodiment of this patent the active domain of the bacterial phosphorylase, PhoQ, will be fused in a gene fusion to a region of a heavy chain antibody cDNA".

As can be appreciated from the context of the general descriptions of the ligand binding domain (as including, e.g., antibodies and antibody fragments) and the signal transforming domain (as including an active domain of an enzyme that has any number of protein modifying functions, e.g., phosphorylation and dephosphorylation), the specific embodiment in the above-cited passage is one where the signal transforming domain is derived from PhoQ.

In view of the above, the applicant submits that the limitation(s) of Claim 21 are supported by the specification as originally filed.

Claim 22 - Claim 22 recites the limitation "sheltered in a genetically engineered bacterial cell". The Examiner asserts that the specification as originally filed does not provide support for this limitation.

Basis for the recited limitation can be found, for example, on page 13, lines 28-29, which explicitly recites a genetically engineered bacterial cell under the heading of "Entities Sheltering Biodetectors".

In view of the above, the applicant submits that the limitation(s) of Claim 22 are supported by the specification as originally filed.

Claim 25 - Claim 25 recites the limitation "said enzymatic signal transforming domain comprises an active domain of PhoQ". The Examiner asserts that the specification as originally filed does not provide support for this limitation.

Basis for the recited limitation can be found, for example, on page 15, lines 29-30, reproduced above under the heading "Claim 21", as well as page 14, lines 23-26:

> "Typically, the signal converting element will be a transmembrane fusion protein composed of an extracellular ligand-binding portion, e.g. an antibody and an intracellular enzymatic portion, which is activated upon binding of the extracellular portion to a selected target.".

As can be appreciated from the above, the fusion of PhoQ and a region of a heavy-chain antibody (page 15, lines 29-30) is a subset of the general transmembrane fusion protein described above, where the intracellular enzymatic portion (enzymatic signal transforming domain) is derived from PhoQ.

In view of the above, the applicant submits that the limitation(s) of Claim 25 are supported by the specification as originally filed.

Claim 26 - Claim 26 recites the limitation "said fusion protein is a fusion of an active domain of PhoQ, and a region of a heavy chain antibody". The Examiner asserts that the specification as originally filed does not provide support for this limitation.

Basis for the recited limitation can be found, for example, on page 15, lines 29-30, reproduced above under the heading "Claim 21". This section provides essentially word-for-word support for the claimed limitation.

In view of the above, the applicant submits that the limitation(s) of Claim 26 are supported by the specification as originally filed.

In view of the above, the applicant submits that rejection of Claims 1-9 and 21-27 under 35 U.S.C. §112, first paragraph is inappropriate and should be withdrawn.

VII. Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-9 and 21-27 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Claim 1

was objected to as lacking proper antecedent basis for "the" detection of a selected substance.

Claim 1 has been amended by the present amendment delete "the". In view of this amendment, the applicant submits that the rejection of Claim 1 under 35 U.S.C. §112, second paragraph, should be withdrawn.

VIII. Rejections under 35 U.S.C. §103

The Examiner has rejected claims 1-9, 22-24 and 27 under 35 U.S.C. §103 as being obvious and unpatentable over Karube, *et al.*, and Sleigh, *et al.*

The Examiner has also rejected claims 21 and 25 under 35 U.S.C. §103 as being obvious and unpatentable over Karube, *et al.*, and Sleigh, *et al.*, as applied to Claims 1-9, and further in view of Miller, *et al.*

Claim 26 has not been rejected by the Examiner under either 35 U.S.C. §102 or 35 U.S.C. §103. The applicant therefore assumes that the Examiner considers Claim 26 to be free of the prior art.

The above rejections are respectfully traversed in view of the following remarks.

A. The Invention

The invention as described by Claim 1 relates to a biodetector for the detection of a selected substance. The biodetector comprises (a) a signal converting element, having an extracellular ligand-specific moiety and an intracellular signal transforming domain, where the extracellular ligand-specific moiety selectively recognizes the selected substance, which recognition activates said intracellular signal transforming domain; (b) a transducer, where the transducer has an inactive and an active form which are distinct from each other, and where the activated intracellular signal transforming domain converts the inactive form of the transducer into the active form of the transducer; and (c) a responsive element, where the responsive element is activated by the active form of the transducer,

resulting in a detectable signal.

The invention as described by Claims 21 and 25 limits the biodetector of Claim 1 to those cases where the signal transforming domain is derived from or comprises an active domain of PhoQ.

B. The Prior Art

Karube, *et al.*, is a short review of different types of biosensors useful for various types of analyses, including clinical, medical and environmental monitoring, industrial process control, and other applications. The biosensors are typically microbial cells incorporating sensing elements for specific substrates. The reference also reviews certain microbial sensor systems that use luminous bacteria and/or luciferase-encoding genes to generate light as a measure of the level and/or presence of the substance the sensor is designed to detect.

As acknowledged by the Examiner, however, Karube, *et al.*, do not teach biosensors with an extracellular ligand-specific moiety and an intracellular signal transforming domain. In fact, nothing in Karube, *et al.*, suggests making a biodetector having these components.

Sleigh, *et al.*, is a chapter on "Signal Transduction" from a cell physiology textbook. It reviews the various types of signal transduction pathways known to naturally exists in cells. For example, Sleigh, et al., describe pathways wherein an extracellular signal molecule binds to a native receptor on the cell surface, resulting in a conformational change of the receptor, which in turn results in the generation of an intracellular signal. Such pathways are fundamental to the biology of all living cells.

Sleigh, *et al.*, neither teach nor provide any motivation to adapt any of the naturally-existing pathways described therein to an engineered biodetector capable of sensing selected analytes, such as the biodetectors encompassed by the pending claims.

Miller, *et al.*, describe the *phoP/phoQ* two-component regulatory system of *Salmonella typhimurium*, and (based on experiments using *phoP* mutants) suggest that this system is responsible for regulating the virulence of *S. typhimurium*. The reference further teaches that the deduced amino acid sequences of *phoP* and *phoQ* gene products are highly similar to other members of bacterial two-component transcriptional regulators that respond to environmental stimuli.

Although the reference suggests applying the experimental results to the development of better vaccines, Miller, *et al.*, do not suggest using the *phoP/phoQ* or any other two-component system in connection with biodetectors or biosensors.

C. Analysis - the prior art does not show any logical reason for combining the references along the lines of the invention

Obviousness requires some logical reason for combining the references at hand; otherwise, the use of the references will entail prohibited hindsight (*e.g.*, In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999); In re Rouffet, 47 USPQ2d 1453 (Fed. Cir. 1998); In re Adams 148 USPQ 742; and In re Sernaker 217 USPQ 1 (Fed. Cir. 1983)).

1. Rejection of Claims 1-9, 22-24 and 27 in view of Karube, *et al.*, and Sleigh, *et al.*

None of the references cited by the Examiner provides any motivation for the making of a biodetector comprising (a) a signal converting element, having an extracellular ligand-specific moiety and an intracellular signal transforming domain, where the extracellular ligand-specific moiety selectively recognizes the selected substance, which recognition activates said intracellular signal transforming domain; (b) a transducer, where the transducer has an inactive and an active form which are distinct from each other, and where the activated intracellular signal transforming domain converts the inactive form of the transducer into the active form of the transducer; and (c) a responsive element, where the responsive element is activated by

the active form of the transducer, resulting in a detectable signal.

As the court stated in In re Dembiczak, *supra*, "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight".

In the present case, the Examiner has not provided any evidence of a motivation to combine the cited references along the lines of the present invention. Accordingly, the applicant submits that the rejection of Claims 1-9, 22-24 and 27 in view of Karube, *et al.*, and Sleigh, *et al.*, is improper and should be withdrawn.

2. Rejection of Claims 21 and 25 in view of Karube, *et al.*, Sleigh, *et al.*, and Miller, *et al.*

As above, none of the references cited by the Examiner provides any motivation for the making of a biodetector as described above, where the signal transforming domain is derived from or comprises an active domain of PhoQ.

It is the Examiner's view that, given the teachings of the prior art (Miller, *et al.*) that PhoQ functions in response to environmental parameters, it would have been obvious to one of skill in the art to make a biosensor as claimed in Claims 21 and 25.

The applicant respectfully disagrees. The observation in Miller, *et al.*, of the fact that two-component system transcriptional regulators respond to environmental stimuli, is merely a recognition of the basic tenet of biology that all biological systems contain mechanisms which let them interact with and respond to their environment. This observation in no way suggests adapting such a two-component system to be part of a biosensor or biodetector as claimed in Claims 21 and 25.

As stated above, absent a motivation to combine the cited references along the lines of the claimed invention, the Examiner is using prohibited hindsight to piece together the prior art to defeat patentability. Accordingly, the applicant submits that the rejection of Claims 21 and 25 in view of Karube, *et al.*, Sleigh, *et al.*, and Miller, *et al.*, is improper and should be withdrawn.

IX. Summary

In view of the foregoing, the applicant submits that the claims pending in the application comply with the requirements of 35 U.S.C. §112 and patentably define over the prior art. A Notice of Allowance is therefore respectfully requested.

The Examiner is encouraged to call the undersigned at (510) 291-6135 to schedule a telephone conference if there are any remaining points of disagreement or if the Examiner feels that such a telephone conference might expedite the prosecution of the subject application.

Respectfully submitted,

Date: December 28, 1999

Charles K. Sholtz
Registration No. 38,615

Correspondence Address:
Howrey & Simon
301 Ravenswood Avenue
Menlo Park, CA 94025